Does cardiorespiratory fitness really influence venous thromboembolism risk?

S.K. KUNUTSOR[*,†], J.A. LAUKKANEN[‡, §, ¶]

[*] National Institute for Health Research Bristol Biomedical Research Centre, University Hospitals Bristol NHS Foundation Trust and University of Bristol, Bristol, UK

[†] Musculoskeletal Research Unit, Translational Health Sciences, Bristol Medical School, University of Bristol, Learning & Research Building (Level 1), Southmead Hospital, Bristol, UK

[‡] Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland

[§] Department of Medicine, Central Finland Health Care District, Jyväskylä, Finland

[¶] Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland

Corresponding author:

Setor K. Kunutsor, Musculoskeletal Research Unit, Translational Health Sciences, Bristol Medical School, University of Bristol, Learning & Research Building (Level 1), Southmead Hospital, Bristol, BS10 5NB, UK; Phone: +44-7539589186; Fax: +44-1174147924; Email address: skk31@cantab.net

Words [971]

References [10]

To the Editor We commend the authors of “Cardiorespiratory fitness and future risk of venous thromboembolism” for their efforts in investigating this important topic. In this elegant analysis, Evensen and colleagues using the Tromsø population-based prospective cohort study, assessed the association between estimated cardiorespiratory respiratory fitness (eCRF) and the risk of incident venous thromboembolism (VTE).[1] A higher eCRF was shown to be associated with reduced total VTE, provoked and unprovoked VTE, pulmonary embolism, as well as deep vein thrombosis. The observed association between eCRF and VTE risk was also independent of body weight status.

The independent and inverse association between CRF, an index for habitual physical activity, and the risk of arterial thrombotic disease (cardiovascular disease, CVD) is very well established.[2, 3] Though emerging evidence suggests that regular physical activity is associated with reduced risk of VTE,[4] with the possibility that high CRF levels may reduce the risk of VTE; data on the nature and magnitude of the relationship between CRF and VTE was non-existent until recently. With the publication of this recent study by Evensen and colleagues,[1] this brings to a total of three studies that have now investigated the association between CRF and VTE risk (**Table**).[1, 5, 6] In the first-ever study to investigate the association between CRF and VTE risk, Zoller and colleagues employed maximal aerobic workload in Watts (W_{max}) using a cycle ergonometric test, as a measure of CRF (named cardiovascular fitness in their study) in a cohort of 773,925 males comprising of 3,005 VTE events.[5] In this study, whereas W_{max} was not associated with VTE risk when adjusted for body mass index (BMI), weight-adjusted W_{max} (W_{max}/kg) was associated with reduced risk for VTE. In a recent study published by our group,[6] we found no strong evidence of an association between CRF and the risk of VTE in 2,249 middle-aged Finnish men who were part of the Kuopio Ischemic Heart Disease (KIHD) prospective cohort study. In the current study by Evensen and colleagues,[1] eCRF was associated with a reduced risk of VTE and this was independent of age (as timescale), sex, smoking, education, and histories of CVD or cancer. Several reasons may account for the discrepant findings in these

three studies and these may include factors related to study designs and populations. Though the event rate was low in the Tromsø and KIHD studies,[1, 6] both studies were adequately powered to evaluate the associations. The average follow-up duration for the current study was relatively short[1] compared to the two previous studies which spanned over more than two decades.[5, 6] Inability to fully examine the impact of adjustment for potential confounding is another potential explanation. Zoller and colleagues only adjusted for BMI and familial factors and could not account for several potential confounders, which they duly acknowledged as a limitation of their analysis.[5] In the current study by Evensen and colleagues,[1] several relevant confounders such as lipids, alcohol consumption, and inflammatory markers (eg, C-reactive protein) were not accounted for. Though all three studies were based in closely related Scandinavian countries, these countries differ considerably in demographic history;[7] hence, the differences in characteristics such as age, sex, as well as genetic background may also account for the inconsistent findings. The study by Zoller and colleagues was based on participants who were aged 18-20 years at study entry,[5] whereas the average age for participants in the other studies was in the 50s.[1, 6] However, the Tromsø Study included both younger and older participants (age range of 30-87 years).[1] Unlike the two previous studies which included only men,[5, 6] the Tromsø Study included both men and women, but did not report estimates separately for both genders which could be attributed to the low event rate in the study sample. Another important factor which could account for the differential findings is the assessment of CRF. Our previous study[6] used the gold standard measure of CRF, which is cardiopulmonary exercise testing (CPX) with maximal oxygen uptake ($VO2_{max}$) measured by ventilatory expired gas analysis[8] and demonstrated no evidence of a significant association. On the other hand, the previous and current studies used surrogate measures of CRF and showed evidence of associations.[1, 5] Evensen and colleagues[1] employed a nonexercise algorithm for CRF, which was based on age, waist circumference, resting heart rate and physical activity index. There are several nonexercise-based algorthims available and they can conveniently estimate CRF in a rapid and inexpensive way especially for large

population settings.[9] Though surrogate measures of CRF correlate strongly with the gold standard measure $VO2_{max}$,[10] a major limitation of these nonexercise-based equations is that they tend to underestimate and overestimate CRF at the top and bottom ends of the distribution, respectively.[9] Though the use of CPX for estimating CRF involves higher levels of proficiency, time constraints, as well as equipment and costs and can be a challenge when employed for large-scale populations, the additional information provided by this method allows for the most accurate and standardized quantification of CRF and hence its use is justified.[9] Nonexercise algorithms do provide reasonable accurate estimates of CRF in large populations, but they cannot replace objective assessments of CRF. Indeed, the study by Evensen and colleagues is among the first to present data on the association between eCRF and VTE risk and adds to the existing limited evidence; however, given some of the limitations which were not acknowledged by the authors, the current findings need to be interpreted with caution. The authors suggest the potential of future studies to evaluate a causal association between CRF and VTE. The observational evidence is not robust enough to attempt a causal investigation yet. Further large-scale observational studies with objective measures of CRF and adjustment for a comprehensive panel of relevant confounders are needed to replicate the current findings. Nevertheless, we applaud the efforts of the authors in putting together this fine study and for providing more evidence on the beneficial effects of CRF on adverse vascular outcomes.

Addendum

Study concept and design: S.K. Kunutsor and J.A. Laukkanen. Acquisition of data: S.K. Kunutsor. Interpretation of data: S.K. Kunutsor and J.A. Laukkanen. Drafting the manuscript: S.K. Kunutsor. Critical revision of the manuscript for important intellectual content: S.K. Kunutsor and J.A. Laukkanen. S.K. Kunutsor is the guarantor of this work, and as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

Funding Sources

Prof. Laukkanen acknowledges support from The Finnish Foundation for Cardiovascular Research, Helsinki, Finland. Dr. Kunutsor acknowledges support from the NIHR Biomedical Research Centre at University Hospitals Bristol NHS Foundation Trust and the University of Bristol. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care. These sources had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Disclosure of Conflict of Interests

S.K. Kunutsor and J.A. Laukkanen have no conflicts of interest

References

1 Evensen LH, Isaksen T, Braekkan SK, Hansen JB. Cardiorespiratory fitness and future risk of venous thromboembolism. *Journal of thrombosis and haemostasis : JTH*. 2019. 10.1111/jth.14619.

2 Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, Sugawara A, Totsuka K, Shimano H, Ohashi Y, Yamada N, Sone H. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *Jama*. 2009; **301**: 2024-35. 10.1001/jama.2009.681.

3 Khan H, Jaffar N, Rauramaa R, Kurl S, Savonen K, Laukkanen JA. Cardiorespiratory fitness and nonfatalcardiovascular events: A population-based follow-up study. *Am Heart J*. 2017; **184**: 55-61. 10.1016/j.ahj.2016.10.019.

4 Kunutsor SK, Makikallio T, Seidu S, De Araujo CG, Dey RS, Blom AW, Laukkanen JA. Physical activity and risk of venous thromboembolism: systematic review and meta-analysis of published observational prospective cohort studies *European Jounal of Epidemiology*. 2019.

5 Zoller B, Ohlsson H, Sundquist J, Sundquist K. Cardiovascular fitness in young males and risk of unprovoked venous thromboembolism in adulthood. *Annals of medicine*. 2017; **49**: 176-84. 10.1080/07853890.2016.1252057.

6 Kunutsor SK, Makikallio TH, Araujo CGS, Jae SY, Kurl S, Laukkanen JA. Cardiorespiratory fitness is not associated with risk of venous thromboembolism: a cohort study. *Scand Cardiovasc J*. 2019: 1-4. 10.1080/14017431.2019.1630748.

7 Athanasiadis G, Cheng JY, Vilhjalmsson BJ, Jorgensen FG, Als TD, Le Hellard S, Espeseth T, Sullivan PF, Hultman CM, Kjaergaard PC, Schierup MH, Mailund T. Nationwide Genomic Study in Denmark Reveals Remarkable Population Homogeneity. *Genetics*. 2016; **204**: 711-22. 10.1534/genetics.116.189241.

8 Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, Forman D, Franklin B, Guazzi M, Gulati M, Keteyian SJ, Lavie CJ, Macko R, Mancini D, Milani RV, American Heart Association Exercise CR, Prevention Committee of the Council on Clinical C, Council on E, Prevention, Council on Peripheral Vascular D, Interdisciplinary Council on Quality of C, Outcomes R. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation*. 2010; **122**: 191-225. 10.1161/CIR.0b013e3181e52e69.

9 Ross R, Blair SN, Arena R, Church TS, Despres JP, Franklin BA, Haskell WL, Kaminsky LA, Levine BD, Lavie CJ, Myers J, Niebauer J, Sallis R, Sawada SS, Sui X, Wisloff U, American Heart Association Physical Activity Committee of the Council on L, Cardiometabolic H, Council on Clinical C, Council on E, Prevention, Council on C, Stroke N, Council on Functional G, Translational B, Stroke C. Importance of Assessing Cardiorespiratory Fitness in Clinical Practice: A Case for Fitness as a Clinical Vital Sign: A Scientific Statement From the American Heart Association. *Circulation*. 2016; **134**: e653-e99. 10.1161/CIR.0000000000000461.

10 Jackson AS, Sui X, O'Connor DP, Church TS, Lee DC, Artero EG, Blair SN. Longitudinal cardiorespiratory fitness algorithms for clinical settings. *Am J Prev Med*. 2012; **43**: 512-9. 10.1016/j.amepre.2012.06.032.

Table. Characteristics of studies assessing the association between cardiorespiratory fitness and venous thromboembolism

Lead Author, Publication Date	Name of study or source of data	Location	Population source	Year of baseline survey	Baseline age range (mean/median) (years)	% male	Average follow-up duration (years)	Assessment of CRF	No. of VTE events	Total participants
Zoller, 2017	Swedish nationwide registries	Sweden	Military enlistment	1972-1990	18-20 (18)	100.0	23-28	Maximal aerobic workload in Watts using a cycle ergonometric test	3,005	773,925
Kunutsor, 2019	KIHD	Finland	Population register	1984-1989	42-61 (53)	100.0	25.2	Maximal oxygen uptake estimated using a respiratory gas exchange analyzer during cycle ergometer exercise tests	144	2,249
Evensen, 2019	Tromsø Study	Norway	Population register	2007-2008	30-87 (56)	46.9	8.5	Nonexercise-based algorithm	176	10,393

CRF, cardiorespiratory fitness; KIHD, Kuopio Ischemic Heart Disease